

REMARKS1. Status of the Claims

Claim 1 was previously pending in the present application. Claims 61-75 are added by way of amendment herein. No new matter is added by way of the present Amendment. Support for new claim 61 can be found in the specification, for example, at page 1, lines 11-20; at page 86, lines 25-30 which references, e.g., page 79, lines 7-12; and at page 86, line 25 through page 89, line 16 which references page 79, lines 7 through page 80, line 12. Support for new claims 62 and 69 can be found in the specification, for example, at page 6, lines 2-3. Support for new claims 63-64 and 70-71 can be found in the specification, for example, at page 6, lines 20-24. Support for new claims 65-66 and 72-73 can be found in the specification, for example, at page 46, lines 16-21. Support for new claims 67-68 and 74-75 can be found in the specification, for example, at page 79, lines 9-12. Therefore, claims 1 and 61-75 are currently pending. Reconsideration of the present application is respectfully requested in view of the amendments above and the remarks below.

2. Rejection Under 35 U.S.C. 112, First Paragraph

Claim 1 is rejected under 35 U.S.C. 112, first paragraph in the Office Action mailed July 12, 2004 (hereafter the "Action") as allegedly not being enabled. The present rejection is respectfully traversed for reasons of record and the reasons discussed below.

The Examiner asserts at page 3, last paragraph of the Action that the claimed invention was tested in xenogeneic mice that do not have cancer. The Examiner further asserts that

allegedly "in a situation where Her-2/Neu is a self-protein, such as in mice that have tumors that express HER-2/Neu, self-tolerance could eliminate T cells that are capable of recognizing Her-2/Neu protein with high avidity" (emphasis added).

Applicant respectfully submits that the Examiner has misconstrued the test of enablement by requiring a working example be provided that demonstrates a particular level or efficacy of the claimed invention.

The test of enablement, however, is whether one reasonably skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (see, e.g., *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)). There is no requirement in the test of enablement that a working example demonstrating a desired level or efficacy of treatment be provided in the specification. "The Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government [e.g., the FDA] have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs" (see, e.g., MPEP 8th Ed, r2.1, 2107.03, Section V, Safety and Efficacy Considerations).

In regard to the enablement requirement, there can be no question that it is met, for an analysis of the Wands factors reveals that the USPTO has failed to set forth a prima facie case that it would require undue experimentation for one skilled in the art to make and use the claimed invention, as discussed below.

(A) The Breadth of the Claims and Nature of the Invention

Claim 1, as amended, is directed to a method of activating CTLs *in vivo*, in an animal having malignant cell that express a her-2/Neu protein, comprising the step of immunizing an animal with the polypeptide of SEQ ID NO:12. Claim 61 is directed to a method of treating a patient having a Her-2/Neu expressing tumor, comprising the step of administering SEQ ID NO:12 to the patient. Thus, the claimed invention entails administration of a polypeptide which is fully disclosed in the specification, including a disclosure of its sequence (SEQ ID NO:12). The specification further discloses a working example of the step of immunizing an animal with the polypeptide of SEQ ID NO:12 (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12).

(B) The State of the Art and the Level of Skill in the Art

The state of the art at the time the application was filed was highly developed such that the step of immunizing an animal with a polypeptide was routine in the art. The level of skill of one of ordinary skill in the art, at the time the application was filed, was high, as apparent from the fact that many practitioners have attained a post-graduate level of education and/or years of experience in the art.

Furthermore, one of ordinary skill in the art could routinely administer a polypeptide having the sequence VMAGVGSPYV (SEQ ID NO:12) to an animal or patient having Her-2/Neu expressing tumor cells using the procedures disclosed in the specification. Thus, no undue experimentation is required for one of ordinary skill in the art to practice the claimed invention.

(C) The Level of Predictability in the Art

The Examiner asserts at page 3, last line, of the Action that it is, "unpredictable that mice having tumors that express HER/Neu would produce CTLs specific for SEQ ID NO:12 with high affinity". The Examiner further asserts at the top of page 4 of the Action, "Since the surviving CTLs would have low affinity to the claimed SEQ ID NO:12, one would not be able to predict that said CTLs with low affinity for SEQ ID NO:12 would be able to eliminate tumor cells in vivo (Sherman et al, of record [Sherman et al. Critical Review in Immunology 18 (1-2): 47-54])".

Applicant respectfully submits that the Examiner has misconstrued the test of enablement, as discussed above, by requiring a working example be provided that demonstrates a particular efficacy of the claimed invention. Also, as discussed above, there is no requirement in the statute for a particular efficacy of the claimed invention and the MPEP states that such matters are to be left to other government agencies such as the FDA.

Furthermore, Sherman et al. does not establish that one would not be able to determine that CTLs would have adequate affinity to the claimed SEQ ID NO:12 nor does Sherman et al. establish that one would doubt that administration of SEQ ID NO:12 would be able to eliminate tumor cells *in vivo*. Sherman et al. states that a, "potential barrier in the identification of T-cell epitopes derived from these proteins [tumor associated proteins] and presented by tumor cells is the fact that these proteins are also expressed at low levels in some normal tissues, and therefore, self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity" (emphasis added).

Thus, Sherman et al. does not teach that self-tolerance will occur. Also, Sherman et al. does not teach that self-tolerance will occur for every peptide used as an immunogen. For example, Sherman et al. discloses that immunization of A2K^b mice with a recombinant strain of vaccinia virus containing a monogyna encoding the sequence of the hu p53.149 peptide prevented growth of EL4 A2K^b p53 tumor cells. Thus, self-tolerance does not eliminate the CTL response for all immunogens expressed at low levels by normal tissues as evidenced by Sherman et al.

Furthermore, as discussed immediately below, immunization of A2.1/K^b transgenic mice with the claimed Her-2/Neu polypeptide of SEQ ID NO:12 results in the specific activation of CTLs *in vivo*, even though the mice express Her-2/Neu at low levels in normal tissues (Sherman et al. teaches that Her-2/Neu is expressed at low levels in normal tissues, for example, at page 47, column 2, lines 4-16). The specification teaches that immunization of A2.1/K^b transgenic mice (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12) specifically activates CTLs *in vivo* wherein the activated CTLs from the immunized mice specifically target malignant cells that express the Her-2/Neu protein *in vitro* (see, e.g., page 86, line 25 through page 89, line 16 which references page 79, lines 7 through page 80, line 12).

Thus, even though the A2.1/K^b transgenic mice express low levels of Her-2/Neu, one of ordinary skill in the art would not doubt that immunization with the Her-2/Neu polypeptide of SEQ ID NO:12 still results in specific activation of CTLs *in vivo*. The specific activation of CTLs *in vivo* in an animal model wherein Her-2/Neu is expressed at low levels, and wherein the activated CTLs target Her-2/Neu tumors *in vitro* demonstrates

that self-tolerance does not eliminate the activated CTLs response to the immunogen SEQ ID NO:12 *in vivo* through self-tolerance. Therefore, the Examiner's assertion that it is allegedly unpredictable that one can specifically activate CTLs which target Her-2/Neu expressing tumors due to self-tolerance as taught by Sherman et al., is without merit and should be withdrawn because the specification demonstrates that, in fact, CTLs were activated *in vivo* in an animal model that expresses low levels of Her-2/Neu by immunization of the animal with the polypeptide of SEQ ID NO:12.

The Examiner next asserts at page 3, last sentence, through the top of page 4, of the Action, that, "unless tested, it is unpredictable that mice having tumors that express Her/Neu would produce CTLs specific for SEQ ID NO:12 with high affinity". Applicant respectfully points out that the claims do not require that immunization with SEQ ID NO:12 "would produce CTLs specific for SEQ ID NO:12 with high affinity".

The Examiner next asserts, starting in the first full paragraph on page 4 of the Action, that one could not extrapolate the *in vitro* tumor cell killing with *in vivo* tumor cell killing because 1) allegedly the characteristics of tumor cell lines *in vitro* are different as compared to primary tumor cells (Freshney et al, Dermer et al, or record) and the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost due to an autochthonous immune response (Cheever et al, of record, column 9, first paragraph), 2) allegedly the *in vitro* and *in vivo* environments are different, and 3) allegedly conditions for targeting tumor cells are different as the tumor cells *in vitro* are continuously exposed to CTLs and cytokines.

Applicants respectfully submit that tumor cell lines are a suitable model system for the correlation of *in vitro* results to *in vivo* conclusions (see, e.g., *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Thus, even if the disclosed example of an *in vitro* testing system is different from an *in vivo* application (i.e., targeting malignant cells that express a Her-2/Neu protein *in vivo*), this difference in and of itself is not sufficient to establish a prima facie case of lack of enablement unless there is reason to doubt the objective truth of the statements contained in the application which must be relied on for enabling support (see, e.g., *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971)).

As discussed above, the Examiner asserts that the expression of a Her-2/Neu, that is originally expressed with initiation of a tumor, could be subsequently lost due to an autochthonous immune response (Cheever et al, of record, column 9, first paragraph) (emphasis added). However, the Examiner fails to provide evidence that an autochthonous immune response does occur, or that the response occurs in all individuals and tumors. Furthermore, the invention is not directed to cells that do not express a Her-2/Neu protein; therefore, the present rejection is without merit and should be withdrawn.

Also as discussed above, the Examiner asserts that the conditions for targeting tumor cells (*in vitro* versus *in vivo*) are different as the tumor cells *in vitro* are allegedly continuously exposed to CTLs and cytokines. However, the Examiner never provides evidence that this alleged difference of continuous exposure to CTLs and cytokines renders the *in vitro* targeting of malignant cells that express a Her-2/Neu

protein an irrelevant model system, or working example, for the targeting of malignant cells that express a Her-2/Neu protein *in vivo*. For example, the Examiner never provides evidence that tumor cells *in vivo* are not also continuously exposed to CTLs and cytokines after immunization with the polypeptide of SEQ ID NO:12.

Next, the Examiner asserts on page 5 of the Action that even if activated CTLs are significantly increased, the therapeutic success allegedly remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells. As discussed above, the claimed invention, as amended, relates to those tumors that do express Her-2/Neu protein. Therefore, the present rejection is without merit and should be withdrawn. Furthermore, as discussed above, the statutory requirements for enablement do not include a requirement for a particular level or degree of efficacy.

(D) The Amount of Direction Provided by the Inventor.

As discussed below, Applicant respectfully submits that the amount of direction provided by the specification was adequate. The specification discloses how to make the polypeptide of SEQ ID NO:12 (see, e.g., page 84, lines 25-37); discloses how to immunize an animal with the polypeptide of SEQ ID NO:12 (see, e.g., page 86, lines 25-30 which references, e.g., page 79, lines 7-12); discloses that CTLs were activated by the immunization; and discloses that, when collected, the activated CTLs specifically target malignant cells that express a Her-2/Neu protein *in vitro* (see, e.g., page 86, line 25 through page 89, line 16 which references page 79, lines 7 through page 80, line 12). The level of direction provided in the specification was enabling at the time of filing because

one of ordinary skill in the art was able to make and use the claimed invention without undue experimentation.

(E) The Existence of Working Examples.

Applicant respectfully submits that the testing of the activated CTLs *in vitro* constitutes a working example relevant to the utility of the claimed invention as discussed below. MPEP 8r1 2164.02 states that, "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention". The use of tumor cell lines was an accepted model system for testing of anti-cancer agents commonly used by the National Cancer Institute at the time the application was filed (see, e.g., *In re Brana*). Furthermore, there is no requirement that a working example be provided in the specification (see, e.g., MPEP 8r1 2164.02). An applicant need not have actually reduced the invention to practice prior to filing. *In Gould v. Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987).

(F) The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure.

Based upon the disclosure, and the knowledge present in the art, Applicant submits that one of ordinary skill in the art would have been able to immunize an animal having malignant cells that express a Her-2/Neu protein *in vivo* with the polypeptide of SEQ ID NO:12 without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (see, e.g., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed.

Cir. 1985)). Therefore, the present rejection should be withdrawn because, in view of the knowledge in the art, Applicant discloses how to make and use the claimed invention in the specification without undue experimentation.

3. Rejection under 35 U.S.C. § 102(b)

Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Grey et al., of record (WO 94/20127). Applicant respectfully traverses the present rejection for reasons of record and for the reasons discussed below. Claim 1, as amended, recites a method of specifically activating CTLs in vivo in an animal having malignant cells that express a Her-2/Neu protein, comprising immunizing the animal with the polypeptide of SEQ ID NO:12. Grey et al. does not teach, for example, specifically activating CTLs *in vivo* in an animal having malignant cells that express a Her-2/Neu protein. Therefore, Grey et al. cannot anticipate the present invention because Grey et al. does not disclose each and every element of the claimed invention. Nor does the reference support the claimed invention. Accordingly, Applicant respectfully submits that the claim is patentable over Grey et al.

CONCLUSION

Claims 1 and 61-75 are pending in the present application. Applicant believes that claims 1 and 61-75 are in condition for allowance and earnestly solicits an early notification of allowance from the Examiner.

The Commissioner is hereby authorized to charge Deposit Account No. 19-0962, should any additional fees be required in this application.

Respectfully submitted,

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